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Induction of xenoreactive CD4+ T-cell anergy by suppressor CD8+CD28- T cells.

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BACKGROUND: The underlying mechanism of immune suppression mediated by regulatory T cells is not completely understood. In previous studies we have shown that antigen-specific human T suppressor cells (Ts) can be generated *in vitro* by multiple rounds of stimulation with allogeneic, xenogeneic, or antigen-pulsed autologous antigen-presenting cells (APC). Human Ts express the CD8+CD28- phenotype and require specific recognition of MHC class I/peptide complexes on the surface of APC to block proliferation of T helper cells (Th). The aim of the present study was to explore the activation requirements of Ts, as well as the nature of Th unresponsiveness to xenogeneic (swine) antigens induced by Ts. **METHODS AND RESULTS:** We investigated whether specific antigenic stimulation of Ts is required for their ability to inhibit early activation of xenoreactive Th (up-regulation of CD40 ligand). Flow cytometry studies indicated that Ts function required specific recognition of MHC class I on the surface of the stimulating APC. However, neither proliferation nor protein synthesis was required for the ability of Ts to inhibit Th. Ts drastically reduced the capacity of xenoreactive Th cells to produce interleukin (IL)-2 in response to the specific APC, without affecting their surface expression of IL-2 receptor. The suppressor effect that Ts exerted on Th proliferation could not be circumvented by CD40 ligation on the surface of the APC but could be reversed by the addition of exogenous IL-2. **CONCLUSION:** These data indicate that induction of anergy of xenoreactive human Th cells upon specific recognition of MHC class I antigens. Hence, Ts may prevent the activation of T cell-mediated immune responses against xenogeneic transplants.

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